Calcific Uremic Arteriolopathy: A Call for Action

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Summary: Calciphylaxis (calcific uremic arteriolopathy [CUA]) is a threatening disease that increasingly is acknowledged as a challenging condition at the interface of nephrology, dermatology, and cardiology. The primary CUA diagnosis is determined most often in nephrology care units because the vast majority of affected cases are detected in patients with advanced or end-stage renal disease. The typical clinical cascade starts with severe pain in initially often inconspicuous skin areas, which might progress to deep tissue ulcerations. Ulcer development is a severe complication with particularly high morbidity and mortality. Unfortunately, there has been a certain stagnancy regarding the slow progress in our understanding of how and why CUA develops. In addition, several important open issues regarding therapy have not been addressed successfully yet. Therefore, the European Renal Association – European Dialysis and Transplant Association (ERA–EDTA) scientific working group Chronic Kidney Disease-Mineral and Bone Disorders (CKD-MBD) has accepted the challenge and has initiated a call for action by defining calciphylaxis as one of the outstanding research targets for the upcoming years.
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Only rough estimates can be made regarding the true incidence and prevalence of calcific uremic arteriolopathy (CUA) in nephrology patient cohorts and no reliable statement can be made if these figures are changing over time. Recent data from the United States points toward an increase in incidence.[1] Based on our experience, the incidence of CUA in dialysis patients is still less than 1% per year and, accordingly, lower than previously reported.[2] Moreover, assessment of calciphylaxis incidence or prevalence always needs to take into account if these figures are truly changing or if awareness of the disease may be increasing and if therefore increasing incidence might be based simply on better diagnosis and reporting. Overall, CUA qualifies as a true rare (orphan) disease (refer to http://www.orpha.net/consor/cgi-bin/index.php). The status of a rare disease also implies that CUA is more than just an exotic example among the long continuum of cardiovascular calcification problems in uremic patients. Such cardiovascular calcifications might present as arterial calcification (both arteriosclerotic and atherosclerotic) or calcific valvular disease, and affect the majority of long-term dialysis patients. Based on the early work of Selye and Berczi[3] in the 1960s, the term *calciphylaxis* first appeared in human medicine. The basal concept about calciphylaxis development by Selye and Berczi is not without obvious discrepancies to what we consider important in CUA pathophysiology nowadays, but nevertheless is very useful to concisely summarize our growing understanding about CUA. Presumably, CUA development requires chronically disturbed background conditions (ie, the breeding ground in the sense of Selye and Berczi's sensitization factors). These sensitization factors must be present for a certain latency or critical period and require a second-hit or final trigger—a challenging factor—to provoke the outbreak of the full-blown disease. Although chronic kidney disease (CKD) is present in most cases of calciphylaxis and therefore CKD is a predominant sensitization factor, the identification of the challenging factors is still incomplete and challenging.

Despite the growing interest in CUA, many improvements in the community's awareness and much better general knowledge in the field in the past 10 years in clinical research has failed to provide an adequate response to the threat associated with CUA. Severely impaired prognosis in terms of survival,[4] plus a dramatically reduced quality of life,[5] together with a high expenditure for the health system (eg, owing to long-term hospitalizations) clearly deserve our attentiveness as caregivers and scientists in charge. Moreover, we speculate that disclosing some of the secrets of CUA might finally help us in our understanding (and with prevention and treatment) of more common vascular calcification conditions such as diabetic, uremic, or senescent calcifying arteriosclerosis.[6]

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We speculate that the rapidly evolving medial and soft-tissue calcifications as seen in the skin of calciphylaxis patients can serve as a high-speed template for arteriosclerotic vascular disease such as Mönckeberg's sclerosis or calcific aortic stenosis.

CALCIPHYLAXIS RESEARCH AND PATIENT CARE: WHERE DO WE STAND AND WHERE DO WE WANT TO GO?

A recent PubMed search (www.pubmed.org) for the term "calciphylaxis" in March 2014 showed approximately 1,000 citations. By using the prespecified filter functions of PubMed we detected a relatively stable and constant yearly rate of publications ranging from 42 to 76 between 2007 and 2013. The number of case reports, case series, and review articles among the publications was remarkably high. This contrasts in a noteworthy way with the low number of articles presenting original work about CUA. This imbalance is prototypic for medical conditions, with a long way to go to close the gap between speculation and evidence. Even more striking is that PUBMED currently lists only 4 articles as clinical trials in the field of calciphylaxis. However, even 4 clinical trials is flattering considering that there are no randomized, controlled, prospective, intervention studies. Performing a randomized, prospective trial in calciphylaxis faces significant difficulties such as the overall low incidence. In addition, the severity of the disease per se together with the high comorbidity burden is challenging for a study set-up. Collecting and analyzing prospective observational noninterventional data on therapeutic approaches together with detailed outcome recordings might help overcome this unacceptable situation. Such an approach can be realized via registry initiatives. European registry activities are ongoing in the United Kingdom and Germany. Access, patient registration, as well as data recording, transfer, and storage are performed via the internet at www.calciphylaxis.net (German registry) or at www.calciphylaxis.org.uk (UK registry). Data monitoring, plausibility checks, and data cleaning are organized centrally in these registries. Registries show genuine weaknesses and limits compared with data generated in randomized trials, but they can provide valuable support for the search of risk factors, the clinical picture, and the course of CUA. We currently are overseeing approximately 220 patients in the German calciphylaxis registry who have been notified over the past 6 years. In terms of therapy, clustering and analyzing data from these 220 patients allows us to summarize a good overview on what currently is regarded as the standard of care in (German) CUA patients. The details are described in later sections. Therefore, as long as interventional, prospectively recorded data are missing, the contribution coming from prospective CUA registry data cannot be overestimated. These registries can provide valuable input to our understanding of calciphylaxis. In consequence, the European Renal Association – European Dialysis and Transplant Association (ERA–EDTA) scientific working group Chronic Kidney Disease-Mineral and Bone Disorders (CKD-MBD) actively is initiating an international calciphylaxis registry in 7 European countries (Belgium, Spain, Portugal, Italy, The Netherlands, Germany, and France): the European Calciphylaxis Network (EuCalNet project) (for details, please see www.calciphylaxis.net). The EuCalNet consortium is planning to initiate an internet-based multilingual registry in which treating physicians can provide patient data on demographics and comorbidities; the clinical picture, including photographic documentation and pain scale reporting; comorbidities; laboratory data of patients at the time of CUA diagnosis; and medical treatments including dialysis, surgeries, and wound management.

Another CUA aspect still remains unsolved: is it really one single disease? We currently assume that it is. However, experts agree that differentiating CUA in terms of lesions size, character, and localization is quite important for outcome. Lesion size may vary from single nodular nonulcerative lesions (Fig. 1) to an

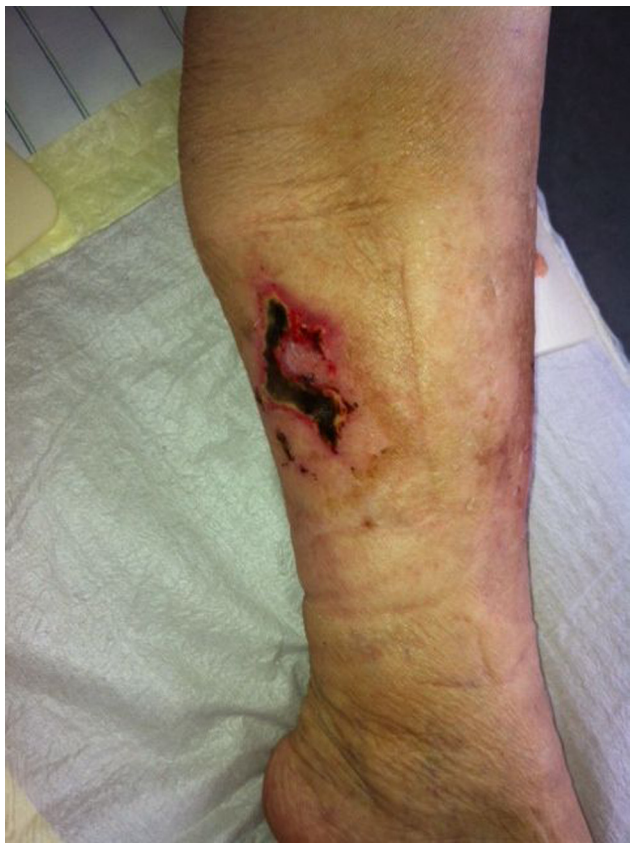

Figure 1. Localized CUA lesion at the lower leg.